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Association of Osteoarthritis with Perfluorooctanoate and Perfluorooctane Sulfonate in NHANES 2003–2008

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Abbreviations: CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; PFAA, perfluoroalkyl acid; PFC, perfluorinated compound; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PPAR, peroxisome proliferator-activated receptor

ABSTRACT

Background: Perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) are persistent, synthetic industrial chemicals. Perfluorinated compounds are linked to health impacts that may be relevant to osteoarthritis, cartilage repair, and inflammatory responses.

Objectives: We investigated whether PFOA and PFOS exposures are associated with prevalence of osteoarthritis, and whether associations differ between men and women.

Methods: We used multiple logistic regression to estimate associations between serum PFOA and PFOS concentrations and self-reported diagnosis of osteoarthritis in persons 20-84 years of age who participated in NHANES from 2003-2008. We adjusted for potential confounders including age, income, and race/ethnicity. Effects by gender were estimated using stratified models and interaction terms.

Results: Those in the highest exposure quartile had higher odds of osteoarthritis compared to those in the lowest quartile (OR for PFOA = 1.55; 95% CI: 0.99, 2.43; OR for PFOS = 1.77; 95% CI: 1.05, 2.96). When stratifying by gender, we found positive associations for women, but not men. Women in the highest quartiles of PFOA and PFOS exposure had higher odds of osteoarthritis compared to those in the lowest quartiles (OR for PFOA = 1.98; 95% CI: 1.24, 3.19) and (OR for PFOS = 1.73; 95% CI: 0.97, 3.10).

Conclusions: Higher concentrations of serum PFOA were associated with osteoarthritis in women, but not men. PFOS was also associated with osteoarthritis in women only, though effect estimates for women were not significant. More research is needed to clarify potential differences in susceptibility between women and men with regard to possible effects of these and other endocrine disrupting chemicals.

Introduction

Perfluoroalkyl acids (PFAAs) are a family of anthropogenic, fluorinated chains of four to fourteen carbon atoms (Lau et al. 2007). The unusual oil- and water-repelling characteristics of these molecules led to their use in over 200 industrial processes and consumer applications, including: emulsifiers and surfactants; protective coatings for textiles, wood, leather, and metal products; non-stick cookware; grease-proof coatings for paper-based food storage containers; fire-retardant foams; and, personal care products (Lau et al. 2007). Due to their wide range of uses and persistent chemical properties, PFAAs have become ubiquitous contaminants of humans and wildlife (Kuklenyik et al. 2005). Evidence of widespread human contamination with PFAAs was first published about 35 years ago (Guy and Taves 1976). More recently, concentrations of specific PFAAs in various environmental media, birds, fish, and humans, have been summarized by Lau et al. (2007). This review of the literature showed that PFAAs have been found in human serum worldwide, and can be measured in wildlife and in fresh and salt water even in remote areas (Lau et al. 2007). These chemicals bioaccumulate, and laboratory data suggest that PFAAs may act as endocrine disrupting chemicals (Jensen and Leffers 2008). Despite the United States Environmental Protection Agency's safety reviews and agreements with some major manufacturers to voluntarily phase-out these chemicals in some locations, use of PFAAs continues and exposure to many perfluorinated compounds, including PFOA and PFOS, remains widespread (Calafat et al. 2007).

Osteoarthritis, the most common form of arthritis, affects approximately 27 million adults in the United States (Lawrence et al. 2008) and disproportionately impacts women, older individuals, and certain racial/ethnic groups. The disease is characterized by degeneration of tissues in the

joints, which leads to chronic pain and joint stiffness. Individuals with osteoarthritis are more likely to report experiencing disability than those without the disease (Botha-Scheepers et al. 2006). The increasing prevalence of osteoarthritis in the United States is likely due, at least in part, to the aging population and concurrent increases in overweight and obesity (Bitton 2009). While the causes of osteoarthritis are not fully understood, inflammation, abnormal calcium homeostasis, and oxidative stress are thought to be involved. In animal and *in vitro* models, PFOA and PFOS have been linked to inflammation (DeWitt et al. 2009, Qazi et al. 2009, Singh et al. 2012), oxidative stress (Eriksen et al. 2010, Qian et al. 2010), and disturbance of calcium homeostasis (Kleszczyński and Składanowski 2011, Liu et al. 2011). In particular, PFOA is hypothesized to increase inflammation through its ability to induce pro-inflammatory cytokines (Singh et al. 2012). Additionally, by binding to PPAR- γ and PPAR- α, PFOA and PFOS could trigger changes in bone metabolism, which could relate to the onset and progression of osteoarthritis symptoms (Innes et al. 2011). A previous study examined the relationships between PFOA and PFOS exposure and osteoarthritis in participants living or working in Ohio and West Virginia communities with PFOA-contaminated drinking water (Innes et al. 2011). In these communities, they found a statistically significant 30% increased odds of self-reported physician-diagnosed osteoarthritis when comparing participants in the highest quartile of PFOA exposure to those in the lowest quartile, whereas they found a negative association for PFOS.

Since the previous study focused on individuals living in highly PFOA-exposed communities (Innes et al. 2011), we aimed to determine if PFOA and PFOS exposures are associated with increased osteoarthritis prevalence in a population with more common exposure levels for PFOS. Our study participants are a representative sample of individuals from the U.S. population who participated in the National Health and Nutrition Examination Survey (NHANES) from 2003

through 2008. We hypothesized that levels of PFOA and PFOS exposure would be associated with the prevalence of osteoarthritis and that associations would differ by gender due to hormonal differences.

Methods

NHANES is conducted by the National Center for Health Statistics, which selects approximately 5,000 study participants annually from the non-institutionalized United States population. NHANES represents the most comprehensive attempt to understand human exposures to chemicals of concern (National Research Council 2006) and has been the sole data source for many cross-sectional studies of associations between chemical exposures and chronic disease. The study participants are a representative sample of the United States civilian, non-institutionalized population. Participants are selected through a multi-stage, probability sampling design. Each of the study participants undergoes a physical examination by a health professional, which includes measurement of height and weight, and completes a series of surveys to ascertain demographic, health, and nutrition information. Various biological samples are also collected for analysis from a random subset of study participants each year. Since 1999, NHANES has operated as a continuous annual survey with data released in two-year cycles. Further details on study design are available from the Centers for Disease Control and Prevention (CDC) (CDC 2011a). The NHANES was reviewed by the National Center for Health Statistics Ethics Review Board and documented consent was obtained from participants. The variables used in our analysis are all publicly available through the CDC.

Exposure

NHANES has annually assessed perfluorinated compounds since 2003 among a subsample of participants. Perfluorinated compound exposures are estimated by measuring the concentrations of 18 perfluorinated chemicals in serum samples collected from a random sample of one third of the study participants age 12 and older (as described by Kuklenyik et al. 2005). In summary, the CDC uses a solid-phase extraction method coupled to high-performance liquid chromatography-tandem mass spectrometry. The limits of detection for PFOA and PFOS are 0.1 and 0.2 μg/g, respectively. At the time of our analyses, laboratory data were available through the 2007-2008 NHANES cycle; we made use of information from 2003-2008 to increase the sample size. We restricted our analyses to persons aged 20-84, the group for which we had osteoarthritis status information and precise age information (in NHANES, the ages of all individuals aged 85 years and older are coded as 85 to ensure anonymity). For categorical models of exposure to PFOA or PFOS, we assigned participants to four exposure categories based on distributions in the study population as a whole. The cut-points for PFOA were: Quartile 1 (≤ 2.95 ng/mL), Quartile 2 (> 2.95– 4.22 ng/mL), Quartile 3 (> 4.22 – 5.89 ng/mL), and Quartile 4 (> 5.89 ng/mL). The cut-points for PFOS were: Quartile 1 (≤ 8.56 ng/mL), Quartile 2 (> 8.56 – 13.59 ng/mL), Quartile 3 (> 13.59 – 20.97 ng/mL), and Quartile 4 (> 20.97 ng/mL).

Outcome

Information on the outcome of interest, osteoarthritis status, was collected by questionnaire via self-report. A previous study documented 81% agreement between a self-report of "definite" osteoarthritis and clinical confirmation (March et al. 1998), which suggests that osteoarthritis is likely to have been accurately reported in most cases. All NHANES participants aged 20 and

older were asked, “has a doctor or other health professional ever told you that you had arthritis?” Individuals who responded affirmatively were asked a follow-up question: “which type of arthritis was it?” Possible answers to the latter question included: rheumatoid arthritis; osteoarthritis; other type of arthritis; unknown type; and decline to answer the question. Individuals who indicated that a doctor had provided a diagnosis of arthritis, but who declined to answer the question about the type of arthritis or indicated that they did not know which type they had were classified as missing, and were excluded from the analyses. Those who indicated that they had rheumatoid arthritis or a form of arthritis other than rheumatoid or osteoarthritis were considered to not have osteoarthritis.

Covariates

Information on potential confounders was obtained from publicly available NHANES data. Potential confounders were selected based on prior reports of associations with PFOA and PFOS exposure levels (Calafat et al. 2007, Nelson et al. 2010) and osteoarthritis (Anderson and Felson 1988, CDC 2011c). We assessed potential confounders as continuous variables unless otherwise noted, including: age; gender (male v. female); poverty status (a ratio of annual family income divided by the federal poverty threshold, calculated by the National Center for Health Statistics); self-reported race/ethnicity (Mexican American, non-Hispanic white, non-Hispanic black, or other, including other Hispanic and multi-racial); daily fat and caloric intake (based on responses during the first of two 24-hour dietary recall surveys); body mass index [weight(kg)/height(m)^2]; self-reported history of bone fractures of the hip, wrist, or spine (yes/no); self-reported participation in moderate or vigorous sports, fitness, or recreational physical activities (yes/no); self-reported smoking status (current, former, never); and for women, self-reported parity (0, 1, or ≥2 offspring). Interpretation of results should consider that further research is needed to

disentangle the relationships among some of these covariates, exposure, and health outcome. For example, those with arthritis may engage in less physical activity.

Statistical Analysis

We used multivariable logistic regression to estimate associations between PFOA, PFOS and odds of osteoarthritis (yes/no). All analyses were conducted separately for PFOA and PFOS. First, we confirmed linear associations between exposure to PFOA or PFOS and odds of osteoarthritis using a test for linear trend. Then we developed models in which the exposures of interest, which were highly right-skewed, were treated as natural logarithm-transformed continuous variables. We developed separate models in which the exposures of interest were treated categorically. We first performed logistic regression with PFOA or PFOS and osteoarthritis without adjustment by any covariates to obtain crude estimates. We then adjusted for sociodemographic factors including age, poverty-income ratio, race/ethnicity, and gender. After eliminating highly correlated dietary and exercise variables, we performed backward model selection using likelihood ratio tests to build fully adjusted models including potential confounders that were statistically significant predictors of the outcome ($p < 0.05$).

We present results for the association between PFOA or PFOS and osteoarthritis based on three models: a crude (unadjusted) model; a model adjusted for sociodemographic factors (age, race/ethnicity, and poverty-income ratio); and a fully adjusted model with adjustment for age, race/ethnicity, and poverty-income ratio as well as variables selected to be associated with osteoarthritis based on the backward model selection.

We used multiplicative interaction terms and stratified models to assess potential effect modification by gender, age (29 – 49 years or 50 – 84 years), and obesity status (BMI ≥ 30 or $<$

30). All models accounted for the complex, multi-stage sampling design of NHANES as recommended by the CDC (CDC 2011b). Stratum, cluster, and subsample weights were included in all logistic regression models using SAS statistical software survey procedures used in previous analyses of NHANES data (e.g. Meeker and Ferguson 2011, You et al. 2011). All analyses were performed using SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC). Estimates were considered statistically significant based on two-tailed p-values < 0.05.

Results

Of 15,562 individuals aged 20-84 who participated in NHANES from 2003-2008, PFOA and PFOS exposure information was available for 4,562 individuals, and 4,102 of these individuals also had osteoarthritis status information. Participants with missing information for one or more model covariates (income, body mass index, smoking, or history of bone fractures) were excluded. Approximately 6% (n=243) of these 4,102 subjects had missing income information, and were excluded from our analyses. Body mass index information was missing for about 1.3% of the remaining subjects (n=50). Smoking information was missing for less than 1% of subjects (n=2, both of whom had already been excluded due to other missing information). Information on history of bone fractures was missing for one individual who had been excluded due to missing income information.

Our study population included similar numbers of males and females, and had a relatively even age distribution (Table 1), and characteristics were similar to the overall NHANES sample of 15,562 individuals who participated during the study time period (data not shown). Compared to females, males had higher exposures to both PFOA (33.4% higher, p<0.001) and PFOS (38.1% higher, p<0.001). Mean serum PFOA and PFOS concentrations also increased with age

(p<0.001), with the exception of a small decline in PFOA in the oldest age group (70-84 years) compared with the next youngest group (Table 1). Exposures also differed by self-reported race/ethnicity for both PFOA and PFOS (p<0.001), with the highest mean PFOA and PFOS concentrations in non-Hispanic whites and non-Hispanic blacks, respectively, and the lowest mean concentrations of both exposures in Mexican-Americans. PFOA and PFOS exposures increased with socioeconomic status as indicated by the poverty/income ratio (PFOA: p=0.012; PFOS: p=0.202). Exposure levels generally also increased with BMI for both exposures, though average concentrations were lower in obese participants than overweight participants. Differences in exposure by smoking status were small, with levels for current smokers 9.0% higher than never smokers for PFOA and 5.0% lower than never smokers for PFOS.

Osteoarthritis cases were more likely to be female, older, Non-Hispanic White, of higher income, and of higher body mass index than controls. Exposure to PFOA and PFOS differed by osteoarthritis status, with cases having higher levels than non-cases. The survey-weighted mean PFOA exposures for cases and non-cases were 5.39 ng/mL (95% CI: 4.91, 5.87 ng/mL) and 4.87 ng/mL (95% CI: 4.59, 5.15), respectively. For PFOS, the survey-weighted mean exposures for cases and non-cases were 24.57 ng/mL (95% CI: 21.49, 27.65 ng/mL) and 21.32 ng/mL (20.05, 22.59 ng/mL), respectively.

In logistic regression models of all participants (males and females), continuous natural logarithm-transformed PFOA and PFOS exposures were positively associated with osteoarthritis prior to adjustment (Tables 2 and 3). However, associations were not statistically significant after full adjustment, and the OR for PFOS was attenuated toward the null. Comparing subjects in the highest quartile to the lowest quartile of serum PFOA and PFOS, we found statistically significant higher odds of osteoarthritis in the crude (unadjusted) models (Tables 2 and 3). The

crude model for PFOA showed increased odds of osteoarthritis with higher exposure. Those in the fourth quartile of PFOA exposure had 62% higher odds (OR = 1.62; 95% CI: 1.10, 2.39) of osteoarthritis than those in the first quartile. The unadjusted association for PFOS showed some evidence of a dose-response relationship. Study participants in the third and fourth quartiles of PFOS exposure had 2.00 and 2.16 times higher odds of osteoarthritis than those in the first quartile (95% CI: 1.27, 3.17 and 1.37, 3.39), respectively.

These results were generally robust to adjustment by covariates in the partially adjusted model (adjusting for age, sex, race/ethnicity, and income) and the fully adjusted model (adjusting for covariates from the partially adjusted model as well as smoking, BMI, physical activity, and history of bone fractures), although some results lost statistical significance. In our partially and fully adjusted models (2 and 3), those in the fourth quartiles of PFOA and PFOS exposure continued to have elevated odds of osteoarthritis compared to those in the first quartiles of exposure (Tables 2 and 3). After full adjustment (model 3), those in the highest quartile of PFOA exposure had a non-significant 1.55 times higher odds of osteoarthritis compared to those in the lowest quartile (95% OR CI: 0.99, 2.43). After full adjustment (model 3), those in the highest quartile of PFOS exposure had a 1.77 times higher odds of osteoarthritis compared to those in the lowest quartile (95% CI: 1.05, 2.96).

In general, fully adjusted ORs were stronger for obese participants compared with non-obese participants (see Supplemental Material, Table S1) though differences were not statistically significant.

Stratified models by gender showed slightly stronger associations in women than in men (Figure 1). Fully adjusted ORs comparing the highest to the lowest quartile of PFOA exposure were 1.98

(95% CI: 1.24, 3.19) for women and 0.82 (95% CI: 0.40, 1.70) for men (Table 2). Corresponding ORs for PFOS were 1.73 (95% CI: 0.97, 3.10) for women and 1.56 (95% CI: 0.54, 4.53) for men (Table 3). These results were consistent with models with an interaction term for sex and exposure as a continuous variable, which also indicated stronger associations for females. In these interaction models, the odds of osteoarthritis were 1.51 times higher ($p = 0.030$) for women than men for PFOA and 1.33 times higher ($p = 0.097$) for PFOS in the fully adjusted model. Interaction models based on quartiles of exposure showed that the odds of osteoarthritis comparing the fourth and first quartiles of exposure were 1.93 times higher ($p = 0.032$) for women than men for PFOA, whereas for PFOS exposure, the odds for women were 1.27 times higher than for men, although not statistically different ($p = 0.403$).

Models stratified by age suggest stronger associations among those age 20 to 49 compared with older participants (age 50 to 84 years) for men and women combined, and among women (see Supplemental Material, Table S2). The ORs comparing the highest to the lowest quartile of PFOA was 4.95 (95% CI: 1.27, 19.4) in younger women, and 1.33 (95% CI: 0.82, 1.16) in older women, and corresponding ORs for PFOS were 4.99 (95% CI: 1.61, 15.4) in younger women, and 1.30 (95% CI: 0.65, 2.60) in older women. Results were not statistically different between older and younger women, or between men and women, and many strata had small sample sizes. Younger women in the highest quartile of PFOA exposure had a 4.95 times higher odds of osteoarthritis compared to those in the lowest quartile of PFOA exposure, after full adjustment (95% CI: 1.27, 19.4). For PFOS, younger women showed a similar increase in the odds of osteoarthritis when comparing those in the highest quartile of exposure to those in the lowest quartile (adj. OR, 4.99; 95% CI: 1.61, 15.4).

Discussion

We found statistically significant associations between PFOA and PFOS and osteoarthritis. Positive associations between both chemicals and osteoarthritis were observed in females, but not males, both before and after adjustment for potential confounders. Women with the highest levels of PFOA and PFOS appeared to have a 1.98 and 1.73 times higher odds of osteoarthritis, respectively, compared to women in the lowest quartiles of exposure to these chemicals. We estimated stronger associations for younger women (age 20 to 49) than older women (age 50 – 84) although these results should be interpreted with caution due to small numbers of osteoarthritis cases when stratified by gender and age. Innes et al. (2011) reported a stronger relationship between PFOA exposure and osteoarthritis in younger men and women compared to older men and women, for whom a diagnosis would likely have taken place closer to the time of blood sampling. This result, and our observation of the strongest associations in younger women, suggests the need for follow-up in future studies that could better assess exposure before diagnosis and investigate differences in susceptibility to PFCs and other endocrine disrupting compounds prior to and following menopause.

Differences in PFOA exposure levels and study population characteristics complicate the comparison of our results to those of Innes et al. (2011). The PFOA exposure reference categories used by Innes et al. encompass the exposures of the majority of our study participants and U.S. residents in general. Therefore, their results do not imply the absence of low-dose, potentially non-monotonic effects of PFOA in the U.S. general population. In contrast to our findings, Innes et al. observed a negative association for PFOS at exposure levels that were quite consistent with those in our study. While sample size limited our ability to test for effect modification by age and obesity status, which was reported by Innes et al., we did not observe

statistically significant differences according to age or obesity in our study population, although there was some suggestion of stronger associations in younger women than older women, and among obese compared with non-obese participants. Further research is needed to determine whether differences between study populations might be explained by differences in exposure, such that very high PFOA exposures might modify effects of PFOS, for example, or by differences related to race/ethnicity or other characteristics that might modify effects of exposure.

We chose to focus on potential effect modification by sex due to previous animal literature suggesting that effects of PFOA and PFOS on osteoarthritis might be hormonally mediated, and evidence that the chemicals might be excreted differently by males and females (Betts 2007). However, other studies did not identify differences in PFOA excretion by gender (Bartell et al. 2009; Brede et al. 2010).

While the previous study was able to focus on age and BMI differences in a population with very high levels of exposure to PFOA, the present study evaluated the associations between PFOA and PFOS and osteoarthritis among a representative sample of the U.S. population. Our findings suggest that females may be more susceptible than males to effects of perfluorinated compounds.

The biological mechanism(s) by which PFOA and PFOS may cause osteoarthritis are not known, but experimental findings suggest they have the potential to mimic and interact with endogenous hormones, increase the expression of pro-inflammatory cytokines, and bind with peroxisome proliferator-activated receptors (PPARs), which are relevant to biological processes that might influence etiology and progression of osteoarthritis. In particular, PFOA and PFOS can bind to PPAR-α and PPAR-ϒ (DeWitt et al. 2009, Vanden Heuvel et al. 2006), which are involved with

regulation of glucose homeostasis, inflammation, and lipid metabolism and storage (Kersten et al. 2000). Very few studies have reported on sex differences between the associations of PFOA or PFOS and health outcomes in humans. However, a recently published prospective cohort study from Denmark that examined the association between in-utero PFOA exposure and risk of overweight at age 20 found a statistically significant association for females, but not for males (Halldorsson et al. 2012).

Limitations of this research include the relatively small sample size, the cross-sectional study design, exposure assessment at a single time point for each participant, self-reported information on the outcome of interest and several covariates, missing data for some study participants, and the lack of information about the date of osteoarthritis onset. The use of exercise as a potential confounder, while included in our fully adjusted model and incorporated in the analysis by Innes et al. (2011), warrants further investigation as arthritis may affect the ability to exercise. Additionally, potential effect modifiers should be examined such as diabetes and many of the characteristics investigated here (e.g., obesity) with a larger sample size. Due to the relatively long half-lives of PFOA and PFOS (Olsen et al. 2007), the single serum samples likely provide reasonable estimates of long-term exposure. Any exposure misclassification would be random and would be unlikely to differ based on disease status. Still, the single serum measurements could represent exposures following osteoarthritis onset, which could have occurred many years prior to the survey.

Another potential limitation of our work is that samples were taken at a single point in time for each participant, and measured concentrations in these samples may not reflect exposures during etiologically relevant time periods. Evidence from NHANES suggests that PFOS levels decreased in the U.S. population during the study period, whereas levels of PFOA have

essentially remained stable (Kato et al. 2011). Thus, if past exposures are more relevant to osteoarthritis than recent exposures, associations based on current PFOS levels may underestimate potential effects.

While the breadth of variables included in NHANES enabled us to examine and adjust for many potential confounders, residual confounding and possible over-adjustment could be sources of bias. Our inclusion of body mass index and prior history of bone fractures, which could be on a causal pathway between endocrine system disruption and development of osteoarthritis, may have introduced bias toward the null.

As new information about the health consequences of PFAAs emerges, patterns of production and usage are changing. Global production of PFOS has dropped considerably compared to 1999 levels following the primary manufacturer's agreement to end production of the chemical, while global production of PFOA has increased during the same period (Lau et al. 2007). Recognizing the growing importance of PFOA, the EPA launched the PFOA Stewardship Program in 2006. Working with the eight leading manufacturers of PFOA, the EPA developed a goal of eliminating usage and emissions of the chemical by 2015 (Lau et al. 2007). As these compounds are being used less, at least in some parts of the world, newer PFAAs are entering the global marketplace, dominated by molecules with shorter carbon chains that may be less persistent (Betts 2007). These substitute compounds may present their own health and environmental hazards, and new evidence shows that certain substitutes can undergo chemical transformations in the environment yielding PFOS and PFOA (Betts 2007). Given the ongoing use of PFAAs and the global scale of human and environmental contamination, better understanding of the potential health effects of these chemicals, and of factors that might be used to identify susceptible subpopulations, could help to inform public health policies aimed at reducing exposures or

associated health impacts. Future research could investigate the health impacts of newer PFAAs and the degree to which certain groups such as women may be particularly susceptible.

Conclusion

Although production and usage of PFOA and PFOS have declined due to safety concerns, human and environmental exposure to these chemicals remains widespread. Better understanding the health effects of these chemicals and identifying any susceptible subpopulations could help to inform public health policies aimed at reducing exposures or associated health impacts. In this cross-sectional study of a representative sample of the adult US population, PFOA and PFOS exposures were associated with higher prevalence of osteoarthritis, particularly in women. To our knowledge, the present analyses represent the first study of the association between perfluorinated compounds and osteoarthritis in a study population representative of the U.S. Future prospective studies are needed to establish temporality and elucidate possible biological mechanisms. Reasons for differences in these associations between men and women, if confirmed, also need further exploration. If replicated, these findings would support reducing exposures to PFOA and PFOS, and perhaps other PFAAs, to reduce the prevalence of osteoarthritis in women, a group that is disproportionately impacted by this common chronic disease.

References

Anderson, JJ, Felson, DT. 1988. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol 128:179-189.

Bartell, SM, Calafat, AM, Lyu, C, Kato, K, Ryan, PB, Steenland, K. 2009. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ Health Perspect 118:222-228.

Betts, KS. 2007. Perfluoroalkyl acids: what is the evidence telling us? Environ Health Perspect 115:A250-A256.

Bitton, R. 2009. The economic burden of osteoarthritis. Am J Manag Care 15:S230-S235.

Botha-Scheepers, S, Riyazi, N, Kroon, HM, Scharloo, M, Houwing-Duistermaat, JJ, Slagboom, E, et al. 2006. Activity limitations in the lower extremities in patients with osteoarthritis: the modifying effects of illness perceptions and mental health. Osteoarthritis Cartilage 14:1104-1110.

Brede, E, Wilhelm, M, Göen, T, Müller, J, Rauchfuss, K, Kraft, M, et al. 2010. Two-year follow-up biomonitoring pilot study of residents' and controls' PFC plasma levels after PFOA reduction in public water system in Arnsberg, Germany. Int J Hyg Environ Health 213:217-223.

Calafat, AM, Wong, L-Y, Kuklenyik, Z, Reidy, JA, Needham, LL. 2007. Polyfluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003-2004 and comparisons with NHANES 1999-2000. Environ Health Perspect 115:1596-602.

Centers for Disease Control and Prevention. 2011a. About the National Health and Nutrition Examination Survey. Available: http://www.cdc.gov/nchs/nhanes/about_nhanes.htm [accessed 14 April 2012].

Centers for Disease Control and Prevention. 2011b. Continuous NHANES Web Tutorial. Task 1: Specify Sampling Parameters in NHANES Using SUDAAN or SAS Survey Procedures. Available: http://www.cdc.gov/nchs/tutorials/nhanes/surveydesign/SampleDesign/intro.htm [accessed 20 April 2012].

Centers for Disease Control and Prevention. 2011c. Osteoarthritis. Available: http://www.cdc.gov/arthritis/basics/osteoarthritis.htm [accessed 14 April 2012].

DeWitt, JC, Shnyra, A, Badr, MZ, Loveless, SE, Hoban, D, Frame, SR, et al. 2009. Immunotoxicity of perfluorooctanoic acid and perfluorooctane sulfonate and the role of peroxisome proliferator-activated receptor alpha. Crit Rev Toxicol. 39:76–94.

Eriksen, KT, Raaschou-Nielsen, O, Sørensen, M, Roursgaard, M, Loft, S, Møller, P. 2010. Genotoxic potential of the perfluorinated chemicals PFOA, PFOS, PFBS, PFNA and PFHxA in human HepG2 cells. Mutat Res 700:39–43.

Guy, WS. Organic Fluorocompounds in Human Plasma: Prevalence and Characterization. In ACS Symposium Series no. 28; American Chemical Society: Washington, DC, 1976.

Halldorsson, TI, Rytter, D, Haug, LS, Bech, BH, Danielsen, I, Becher, G, et al. 2012. Prenatal Exposure to Perfluorooctanoate and Risk of Overweight at 20 Years of Age: A Prospective Cohort Study. Environ Health Perspect 120:668-673.

Innes, KE, Ducatman, AM, Luster, MI, Shankar, A. 2011. Association of osteoarthritis with serum levels of the environmental contaminants perfluorooctanoate and perfluorooctane sulfonate in a large appalachian population. Am J Epidemiol 174:440-450.

Jensen and Leffers. 2008. Emerging endocrine disrupters: perfluoroalkylated substances. International journal of andrology 31:161-169.

Kato, K, Wong, L-Y, Jia, LT, Kuklenyik, Z, Calafat, AM. 2011. Trends in exposure to polyfluorinated chemicals in the U.S. Population: 1999-2008. Environ Sci Technol 45:8037-8045.

Kersten, S, Desvergne, B, Wahli, W. Roles of PPARs in health and disease. Nature 405:421-424.

Kleszczyński, K, Składanowski, AC. 2011. Mechanism of cytotoxic action of perfluorinated acids. III. Disturbance in $Ca^{2}+$ homeostasis. Toxicol Appl Pharmacol 251:163-168.

Kuklenyik, Z, Needham, LL, Calafat, AM. 2005. Measurement of 18 perfluorinated organic acids and amides in human serum using on-line solid-phase extraction. Anal Chem 77:6085-6091.

Lau, C, Anitole, K, Hodes, C, Lai, D, Pfahles-Hutchens, A, Seed, J. 2007. Perfluoroalkyl acids: a review of monitoring and toxicological findings. Toxicol Sci 99:366-394.

Lawrence, RC, Felson, DT, Helmick, CG, Arnold, LM, Choi, H, Deyo, RA, et al. 2008. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 58:26-35.

Liu, X, Jin, Y, Liu, W, Wang, F, Hao, S. 2011. Possible mechanism of perfluorooctane sulfonate and perfluorooctanoate on the release of calcium ion from calcium stores in primary cultures of rat hippocampal neurons. Toxicol In Vitro 25:1294-1301.

March, LM, Schwarz, JM, Carfrae, BH, Bagge, E. 1998. Clinical validation of self-reported osteoarthritis. Osteoarthritis Cartilage 6:87-93.

Meeker, JD, Ferguson, KK. 2011. Relationship between urinary phthalate and bisphenol A concentrations and serum thyroid measures in U.S. adults and adolescents from the National Health and Nutrition Examination Survey (NHANES) 2007-2008. Environ Health Perspect 119:1396-1402.

National Research Council. 2006. U.S. and International Biomonitoring Efforts. In: Human Biomonitoring for Environmental Chemicals. Washington, DC: National Academy Press, 31.

Nelson, JW, Hatch, EE, Webster, TF. 2010. Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general U.S. population. Environ Health Perspect 118:197–202.

Olsen, GW, Burris, JM, Ehresman, DJ, Froehlich, JW, Seacat, AM, Butenhoff, JL, et al. 2007. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect 115:1298-1305.

Qazi, MR, Bogdanska, J, Butenhoff, JL, Nelson, BD, DePierre, JW, Abedi-Valugerdi, M. 2009. High-dose, short- term exposure of mice to perfluorooctanesulfonate (PFOS) or perfluorooctanoate (PFOA) affects the number of circulating neutrophils differently, but enhances the inflammatory responses of macrophages to lipopolysaccharide (LPS) in a similar fashion. Toxicology 262:207–214.

Qian, Y, Ducatman, A, Ward, R, Leonard, S, Bukowski, V, Lan Guo ,N, et al. 2010. Perfluorooctane sulfonate (PFOS) induces reactive oxygen species (ROS) production in human microvascular endothelial cells: role in endothelial permeability. J Toxicol Environ Health A 73:819–836.

Singh, TS, Lee, S, Kim, HH, Choi, JK, Kim, SH. 2012. Perfluorooctanoic acid induces mast cell-mediated allergic inflammation by the release of histamine and inflammatory mediators. Toxicol Lett 210:64-70.

Vanden Heuvel, JP, Thompson, JT, Frame, SR, Gillies, PJ. 2006. Differential activation of nuclear receptors by perfluorinated fatty acid analogs and natural fatty acids: a comparison of human, mouse, and rat peroxisome proliferator-activated receptor-alpha, -beta, and -gamma, liver X receptor-beta, and retinoid X receptor-alpha. Toxicol Sci 92:476-489.

You, L, Zhu, X, Shrubsole, MJ, Fan, H, Chen, J, Dong, J, et al. 2011. Renal function, bisphenol A, and alkylphenols: results from the National Health and Nutrition Examination Survey (NHANES 2003-2006). Environ Health Perspect 119:527-533.

Table 1. Characteristics of Study Population

Characteristic	N (% within group)	Osteoarthritis Cases N (%)	PFOA, weighted mean (ng/mL)[a]	PFOS, weighted mean (ng/mL)[a]
Overall	4,102 (100)	365 (100)	4.83	21.23
Sex				
Female	2,068 (50.4)	238 (65.2)	4.22	18.17
Male	2,034 (49.6)	127 (34.7)	5.63	25.10
Age				
20-29	825 (20.1)	4 (1.1)	4.69	17.46
30-39	728 (17.8	14 (3.8)	4.73	18.68
40-49	687 (16.8)	31 (8.5)	4.85	20.96
50-59	578 (14.1)	56 (15.3)	5.13	24.43
60-69	620 (15.1)	105 (28.8)	5.48	26.88
70-84	664 (16.2)	155 (42.5)	4.94	27.32
Race/Ethnicity				
Mexican American	816 (19.9)	30 (8.2)	3.71	15.11
Other Hispanic	246 (6.0)	11 (3.0)	4.81	17.95
Non-Hispanic White	2,017 (49.2)	271 (74.2)	5.16	22.12
Non-Hispanic Black	861 (21.0)	42 (11.5)	4.53	24.73
Other	162 (4.0)	11 (3.0)	4.42	21.11
Poverty/Income Ratio				
Below Poverty Line	712 (17.4)	40 (11.0)	4.04	17.19
100-200% Poverty Line	1,075 (26.2)	96 (26.3)	4.56	21.08
> 200% Poverty Line	2,072 (50.5)	205 (56.2)	5.20	22.69
Unknown	243 (5.9)	24 (6.6)	4.92	20.40
Body Mass Index				
Underweight (≤18.5)	69 (1.7)	1 (0.3)	4.13	19.73
Normal Weight (18.5-25)	1,163 (28.4)	70 (19.2)	4.72	20.06
Overweight (25-30)	1,458 (35.5)	125 (34.2)	5.19	22.80
Obese (≥ 30)	1,357 (33.1)	161 (44.1)	4.87	21.92
Unknown	55 (1.3)	8 (2.2)	3.31	19.03
Smoking Status				
Never	2,163 (52.7)	170 (46.6)	4.78	21.37
Former	1,041 (25.4)	149 (40.8)	4.93	23.35
Current	896 (21.8)	46 (12.6)	5.21	20.31
Unknown	2 (0.1)	0 (0.0)	5.77	25.62
History of Bone Fractures				
Yes	467 (11.38)	73 (20.0)	5.31	23.01
No	3,634 (88.59)	292 (80.0)	4.86	21.61
Unknown	1 (0.02)	0 (0.0)	4.24	17.43
Vigorous Physical Activity				
Yes	1,085 (26.45)	44	5.00	20.75
No	3,017 (73.55)	321	4.75	21.55
Moderate Physical Activity				
Yes	2,155 (52.54)	175 (47.9)	4.98	22.00
No	1,946 (47.4)	190 (52.1)	4.83	21.12
Unknown	1 (0.02)	0 (0.0)	5.60	40.40

[a]Means are arithmetic means. Overall ranges: PFOA 0.07-104.00, PFOS 0.14-435.00

Table 2. Weighted Associations Between PFOA Exposure and Self-Reported Osteoarthritis in United States Adults Aged 20-84

	Female and Males (N=3,809)			Females (N=1,921)			Males (N=1,888)		
Exposure	*Crude OR (95% CI)*	*Adjusted OR 1[a] (95% CI)*	*Adjusted OR 2[b] (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR 1[a] (95% CI)*	*Adjusted OR 2[b] (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR 1[a] (95% CI)*	*Adjusted OR 2[b] (95% CI)*
Quartile 1	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Quartile 2	1.60* (1.03, 2.50)	1.36 (0.84, 2.21)	1.32 (0.78, 2.23)	2.24** (1.43, 3.51)	1.45 (0.84, 2.50)	1.44 (0.80, 2.62)	0.93 (0.45, 1.92)	1.07 (0.48, 2.36)	0.97 (0.42, 2.27)
Quartile 3	1.42 (0.93, 2.17)	1.18 (0.73, 1.90)	1.20 (0.72, 2.00)	1.93** (1.19, 3.14)	1.16 (0.68, 1.96)	1.18 (0.67, 2.08)	1.01 (0.55, 1.85)	1.04 (0.50, 2.16)	0.98 (0.46, 2.08)
Quartile 4	1.62* (1.10, 2.39)	1.45 (0.97, 2.17)	1.55 (0.99, 2.43)	3.71** (2.45, 5.62)	1.87** (1.22, 2.87)	1.98** (1.24, 3.19)	0.70 (0.38, 1.31)	0.80 (0.40, 1.59)	0.82 (0.40, 1.70)
Continuous[c]	1.28 (1.05, 1.55*	1.17 (0.96, 1.42)	1.20 (0.96, 1.49)	2.03** (1.58, 2.61)	1.37* (1.03, 1.71)	1.35* (1.02, 1.79)	0.84 (0.65, 1.08)	0.89 (0.68, 1.18)	0.89 (0.67, 1.19)

Results for each gender were obtained from stratified models. -

[a] Adjusted OR 1: Age (continuous), Race/Ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican American, Other Race / Multi-Ethnic), - Socioeconomic Status (poverty-income ratio, continuous) -

[b] Adjusted OR 2: Variables above, and: Smoking (Never, Former, Current), Body Mass Index (continuous), Vigorous Recreational Activity - (yes/no), Prior Hip, Wrist, or Spine Fracture (yes/no) -

[c] ORs represent the relative odds of osteoarthritis associated with a 1-unit increase in ln-transformed PFOA. -

** $p<0.01$ * $p<0.05$ -

TABLE 3. Weighted Associations Between PFOS Exposure and Self-Reported Osteoarthritis in United States Adults Aged 20-84

	Female and Males (N=3,809)			Females (N=1,921)			Males (N=1,888)		
Exposure	*Crude OR (95% CI)*	*Adjusted OR 1[a] (95% CI)*	*Adjusted OR 2[b] (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR 1[a] (95% CI)*	*Adjusted OR 2[b] (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR 1[a] (95% CI)*	*Adjusted OR 2[b] (95% CI)*
Quartile 1	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Quartile 2	1.14 (0.67, 1.92)	1.02 (0.59, 1.75)	1.04 (0.58, 1.85)	1.11 (0.61, 2.03)	0.89 (0.48, 1.67)	0.88 (0.46, 1.70)	1.69 (0.57, 5.05)	1.43 (0.46, 4.39)	1.32 (0.41, 4.25)
Quartile 3	2.00** (1.27, 3.17)	1.80* (1.08, 3.00)	1.99* (1.14, 3.49)	2.60** (1.46, 4.63)	1.74 (0.92, 3.27)	1.92 (0.98, 3.75)	2.20 (0.77, 6.30)	1.90 (0.63, 5.76)	1.86 (0.55, 6.25)
Quartile 4	2.16** (1.37, 3.39)	1.57 (0.97, 2.54)	1.77* (1.05, 2.96)	3.31** (1.98, 5.54)	1.54 (0.90, 2.66)	1.73 (0.97, 3.10)	2.52 (0.98, 6.50)	1.61 (0.62, 4.18)	1.56 (0.54, 4.53)
Continuous[c]	1.37** (1.12, 1.67)	1.09 (0.90, 1.32)	1.15 (0.94, 1.40)	1.75** (1.37, 2.23)	1.14 (0.90, 1.46)	1.22 (0.94, 1.58)	1.34 (0.97, 1.83)	0.95 (0.74, 1.23)	0.95 (0.73, 1.23)

Results for each gender were obtained from stratified models. -

[a] Adjusted OR 1: Age (continuous), Race/Ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican American, Other Race / Multi-Ethnic), - Socioeconomic Status (poverty-income ratio, continuous) -

[b] Adjusted OR 2: Variables above, and: Smoking (Never, Former, Current), Body Mass Index (continuous), Vigorous Recreational Activity - (yes/no), Prior Hip, Wrist, or Spine Fracture (yes/no) -

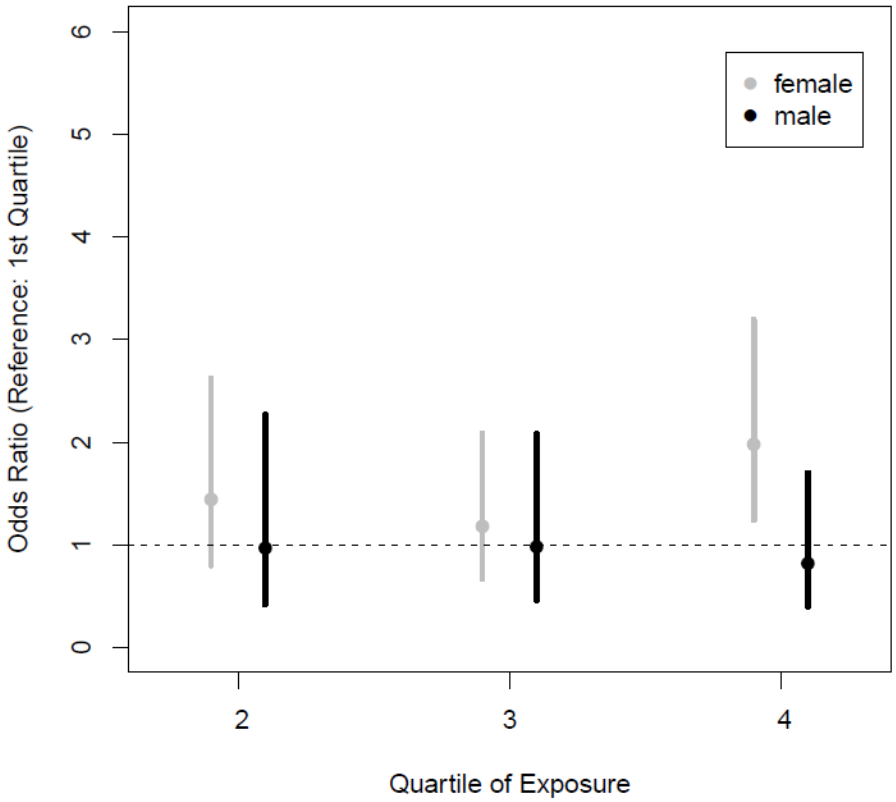
[c] ORs represent the relative odds of osteoarthritis associated with a 1-unit increase in ln-transformed PFOA. -

** $p<0.01$ * $p<0.05$ -

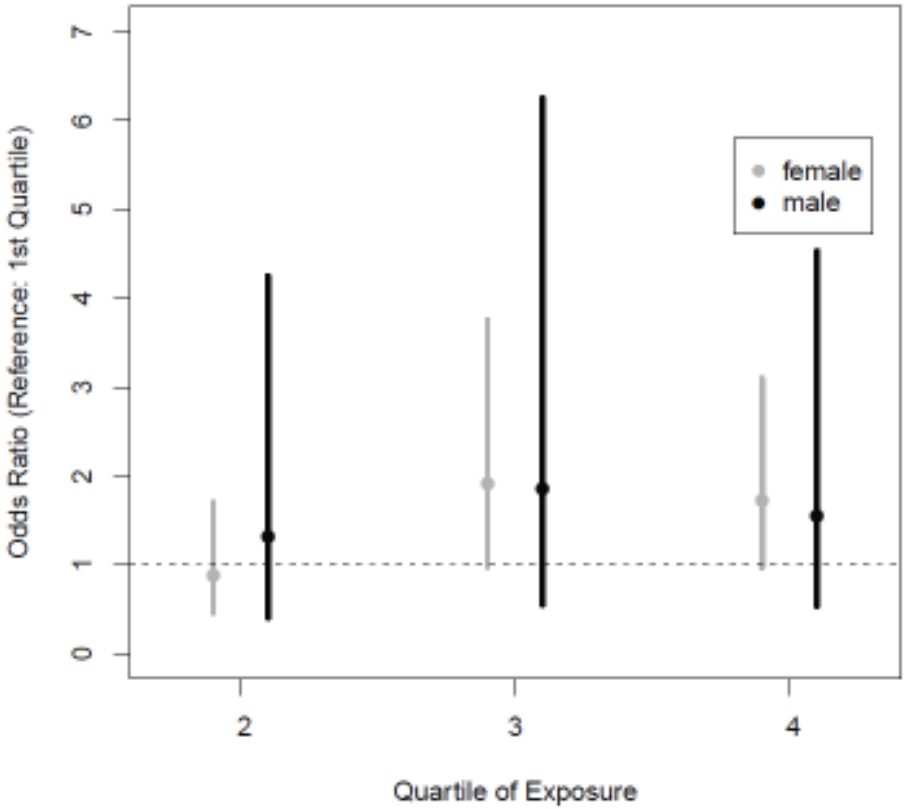
Figure Legend

Figure 1. Associations between PFOA (left) and PFOS (right) exposure quartile (comparing to the first quartile) and odds of osteoarthritis, by gender. Points and vertical lines represent effect estimates and 95% confidence intervals from fully adjusted, gender-stratified models, adjusting for age, race/ethnicity, poverty-income ratio, smoking, body mass index, vigorous recreational activity, and prior fracture (hip, wrist, or spine).

PFOA


female
male
Odds Ratio (Reference: 1st Quartile)
0
1
2
3
4
5
6
2
3
4
Quartile of Exposure

PFOS


female
male
Odds Ratio (Reference: 1st Quartile)
0
1
2
3
4
5
6
7
2
3
4
Quartile of Exposure